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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    89.51      89.93

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -20.28     -20.28

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    89.51      89.93

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -20.28     -20.28

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STRUCTURE FILE UPDATES:   12 MAR 2007  HIGHEST RN 926069-79-6
DICTIONARY FILE UPDATES:  12 MAR 2007  HIGHEST RN 926069-79-6

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predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> E "ROTIGOTINE"/CN 25
E1            1     ROTI-BLOCK/CN
E2            1     ROTIGAPTIDE/CN
E3            1 --> ROTIGOTINE/CN
E4            1     ROTIGOTINE HYDROCHLORIDE/CN
E5            1     ROTIHIBIN A/CN
E6            1     ROTIHIBIN B/CN
E7            1     ROTILAN/CN
E8            1     ROTILANE/CN
E9            1     ROTIMAC/CN
E10           1     ROTIORIN/CN
E11           1     ROTIORINE/CN
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E12          1     ROTIORINOL A/CN
E13          1     ROTIORINOL B/CN
E14          1     ROTIORINOL C/CN
E15          1     ROTISORB/CN
E16          1     ROTKLEE ACTIV TABLETS/CN
E17          1     ROTKLEE TABLETS/CN
E18          1     ROTO 80/CN
E19          1     ROTOCAL/CN
E20          1     ROTOCIDE/CN
E21          1     ROTOFLEX/CN
E22          1     ROTOFLEX RESIST GOLDBRONZE/CN
E23          1     ROTOFRESH/CN
E24          1     ROTOIC ACID/CN
E25          1     ROTOKAL/CN

=> S E3
L5           1 ROTIGOTINE/CN

=> DIS L5 1 IDE
THE ESTIMATED COST FOR THIS REQUEST IS 1.95 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L5   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   99755-59-6  REGISTRY
ED   Entered STN:  18 Jan 1986
CN   1-Naphthalenol, 5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-,
     (6S)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   1-Naphthalenol, 5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-,
     (S)-
OTHER NAMES:
CN   (-)-N 0437
CN   N 0923
CN   Rotigotine
CN   SPM 962
FS   STEREOSEARCH
MF   C19 H25 N O S
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, ANABSTR, BEILSTEIN*, BIOSIS, CA, CAPLUS, CBNB,
       CIN, DDFU, DRUGU, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, PATDPASPC,
       PHAR, PROMT, PROUSDDR, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)

Absolute stereochemistry.  Rotation (-).
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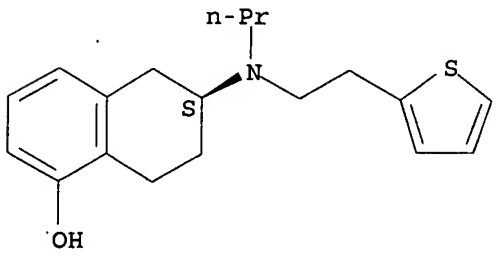


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

            115 REFERENCES IN FILE CA (1907 TO DATE)
              5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
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115 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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=> file caplus biosis medline embase
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         7.80      97.73

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                         0.00     -20.28

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FILE 'EMBASE' ENTERED AT 14:16:06 ON 13 MAR 2007
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=> s rotigotine or neupro or n-0923 or 99755-59-6
L6          510 ROTIGOTINE OR NEUPRO OR N-0923 OR 99755-59-6

=> s chloride(a)salt
L7         6282 CHLORIDE(A) SALT

=> s l6(s)l7
L8            1 L6(S) L7

=> d ti au abs so py

L8   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Iontophoretic delivery of rotigotine for the treatment of Parkinson's
     disease
IN   Wolff, Hans-Michael; Bouwstra, Johanna Aaltje; Li, Gai Ling; Nugroho,
     Akhmad Kharis
AB   By using a composition comprising rotigotine 0.5 to 3 mg/mL and at
     least one chloride salt in a concentration of 1 to 140
     mmol/L, the composition having a pH of 4 to 6.5 in a iontophoretic device for
     the treatment of Parkinson's disease, it became possible to obtain a
     rotigotine flux across the human stratum corneum which was higher
     than the one previously obtained with conventional passive diffusion
     systems.
SO   Eur. Pat. Appl., 11 pp.
     CODEN: EPXXDW
PY   2004
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=> s composition
L9 2912472 COMPOSITION

=> s l6(s)l9
L10 10 L6(S) L9

=> d ti au abs so py 1-10

L10 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
TI Pharmaceutical composition for the treatment of disorders of sexual desire
IN Ceci, Angelo; Mendla, Klaus
AB The invention relates to the use of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety, or a tautomer, a pharmaceutically acceptable salt, solvate, or physiol. functional derivative thereof for the manufacture of a medicament for the for the treatment of sexual desire disorders. A tablet contained a carbomethoxydichlorophenyltropane derivative 1.00, mannitol 121.50, maize starch 79.85, highly dispersed silicon dioxide 2.3, anhydrous 2.30, polyvidon k25 2.35, magnesium stearate and 3.00 mg.
SO PCT Int. Appl., 19pp.
CODEN: PIXXD2
PY 2007

L10 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
TI Pharmaceutical compositions containing combination of dopamine agonists with GABAA and GABAB agonists for treating drug addiction
IN Qi, Hua
AB The title compound preparation is prepared from effective ingredients including (by weight%) one or more non-ergot dopamine (DA) receptor agonists 0.001-30, and one or more γ-aminobutyric acid A (GABAA) receptor agonists or γ-aminobutyric acid B (GABAB) receptor agonists 99.009-65, and adjuvants as balance. The inventive compound preparation is available in the form of capsule, granule, tablet, or sustained-release preparation The preparation has the advantages of low cost, good safety, low toxicity and adverse side effect, and being capable of markedly shortening withdrawal time and alleviating or partially eliminating psychol. craving for drug, and can be used for treating drug addiction.
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 10pp.
CODEN: CNXXEV
PY 2006

L10 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
TI Pharmaceutical compositions comprising an agent with serotonin receptor modulating activity for sleep disorders
IN Rariy, Roman V.; Heffernan, Michael
AB Pharmaceutical compns. are provided for the pharmacol. treatment of breathing disorders and, more specifically, to compns. containing agents having serotonin receptor modulating activity for the alleviation of sleep apnea (central and obstructive) and other sleep-related breathing disorders wherein the active ingredients are released such as to extend effective blood plasma concns. across the period of sleep. For example, ondansetron immediate release tablets were prepared containing ondansetron HCl dihydrate 9.98 mg, lactose 29.14 mg, Prosolv 50 29.14 mg, Ac-Di-Sol 3.75 mg, SDS 1.5 mg, Aerosil 0.75 mg, and Mg stearate 0.75 mg. Ondansetron immediate release tablets were then coated with Eudragit L100/S100 blend to obtain delayed release tablets.
SO PCT Int. Appl., 57 pp.

CODEN: PIXXD2
PY 2006

L10 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
TI Compositions for controlling drug delivery from silicone adhesive blends
IN Houze, David
AB Compns. and methods for controlling transdermal drug delivery, particularly of amine-functional and basic drugs, comprising a blend of a first silicone-based polymer having a reduced silanol concentration and a second silicone-based polymer have a substantial or high silanol concentration The blend of such silicone-based polymers, particularly pressure-sensitive silicone adhesives, provides sufficient drug solubility and reduced initial drug delivery onset to permit a prolonged delivery duration at a substantially zero-order rate of delivery. Thus, fentanyl permeation was slowed as the silanol content of the silicone adhesive matrix increased.
SO U.S. Pat. Appl. Publ., 8 pp.
CODEN: USXXCO
PY 2005
2005
2006

L10 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
TI Iontophoretic delivery of rotigotine for the treatment of Parkinson's disease
IN Wolff, Hans-Michael; Bouwstra, Johanna Aaltje; Li, Gai Ling; Nugroho, Akhmad Kharis
AB By using a compn. comprising rotigotine 0.5 to 3 mg/mL and at least one chloride salt in a concentration of 1 to 140 mmol/L, the compn. having a pH of 4 to 6.5 in a iontophoretic device for the treatment of Parkinson's disease, it became possible to obtain a rotigotine flux across the human stratum corneum which was higher than the one previously obtained with conventional passive diffusion systems.
SO Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
PY 2004
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L10 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
TI Transdermal delivery rate control using amorphous pharmaceutical compositions
IN Morgan, Timothy Matthias; Wilkins, Nina Frances; Klose, Kathryn Traci-Jane; Finnin, Barrie Charles; Reed, Barry Leonard
AB A pharmaceutical composition for transdermal delivery comprising one or more physiol. active agents; one or more dermal penetration enhancers; and a volatile pharmaceutically acceptable carrier comprising a volatile solvent; and wherein the physiol. active agent and dermal penetration enhancer form an amorphous deposit upon evaporation of the volatile carrier,

said amorphous deposit forming a reservoir within the stratum corneum; and wherein the composition has a release rate profile of physiol. active agent so as to provide a ratio of the maximum concentration (Cmax) to the average concentration (Cavg) for the physiol. active agent over the dosage interval within the range of 1 to 10. Examples are provided of testosterone, granisetron, buspirone and fentanyl dermal permeation enhancement by various agents including octyl salicylate and nonyl dioxolane.

SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2

PY 2003
2003
2004
2005
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2006
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L10 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

TI Trans-epicutaneous administration of rotigotine for treating restless leg syndrome

IN Lauterbach, Thomas; Schollmayer, Erwin

AB The invention relates to a trans-epicutaneous pharmaceutical compn. containing rotigotine for effective treatment of Restless Leg Syndrome (RLS), especially in the form of a transdermal therapeutic system (TDS) based on acrylate or silicone having a surface of 2.5-20 cm2 and containing 1.125 9.0 mg/cm2 rotigotine as an active component against Restless Leg Syndrome, which, according to the International Restless Leg Syndrome Study Group (IRLSSG) Rating Scale, results in an improvement in the conditions of human Restless Leg Syndrome patients in comparison with a placebo treatment of 2 units or more, after administration over a period of time of at least 8 days. Thus 264 g polyacrylate solution containing 50% solid matter was mixed homogeneously with 66 g 50% Eudragit E100 in ethylacetate and 36 g oleyl alc. 89.65 G rotigotine in 200 mL methylethyl ketone was mixed with the homogenizate; the drug containing mixture was applied onto a siliconized polyester foil and dried ant 50°C; the result was a 60 g/m2 layer; the foil was cashed with a cover film, cut and packed.

SO PCT Int. Appl., 40 pp.
CODEN: PIXXD2

PY 2003
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L10 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

TI Use of an immediate-release powder in pharmaceutical and nutraceutical compositions

IN Besse, Jerome; Besse, Laurence

AB The present invention relates to the use of a powder comprising at least one active substance, at least one surfactant, at least one wetting agent and at least one diluent, for preparing a pharmaceutical or nutraceutical composition, this composition allowing rapid and immediate release of the active substance. Granules containing phloroglucinol 10, sorbitol 89, and propylene

glycol 1% were prepared
SO U.S. Pat. Appl. Publ., 5 pp.
CODEN: USXXCO
PY 2003
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L10 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
TI combination of a CB1 receptor antagonist and a brain dopaminergic neurotransmission activator, pharmaceutical compositions containing them, and their use in the treatment of Parkinson's disease
IN Benavides, Jesus; Boccio, Daniel; Henin, Yvette; Piot, Grosjean Odile
AB The invention discloses the combination of one or more azetidine derivative CB1 antagonists and one or more substances which activate dopaminergic neurotransmission in the brain, as well as pharmaceutical compns. containing them and their use for the treatment of Parkinson's disease. Methods for azetidine derivative preparation are described.
SO Fr. Demande, 96 pp.
CODEN: FRXXBL
PY 2003
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L10 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
TI Pharmaceutical composition for administering N-0923 in depot form
IN Rimpler, Stephan; Grapatin, Sabine; Krein, Cliff; Thelen, Markus
AB The invention relates to a pharmaceutical compn. for administering the dopamine agonist N-0923 in depot form. A depot of N-092 is formed which achieves a therapeutically significant plasma level over a period of at least 24 h after administration to a patient. As a result of poor oral bio-availability and the short plasma half-life, N-0923 was previously administered either by an i.v. drip or by transdermal systems. The inventive prepns. are oily suspensions, containing the active ingredient N-0923 in a solid phase, in addition to anhydrous pharmaceutical prepns. of N-0923. The compns. can contain other antiparkinsonian agents. Thus a continuous phase was prepared from 1411.2 Myglycol 812 and 14.4 g Imwitor 312 at 80°C; the clear solution was filtered and cooled to room temperature N-0923 hydrochloride was crystallized, 12 g crystals were added to 1188 g of the above solution, homogenized at 10, 000 rpm and filled in brown vials. The filled vials were autoclaved; less than 0.5% of the active substance decomposed during heat sterilization. Rats and cynomolgus monkeys were injected with the product and plasma levels measured.

SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
PY 2002
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=> s iontophore?
L11 29354 IONTOPHORE?

=> s l6 and l11
L12 20 L6 AND L11

=> d ti au abs so py 1-20

L12 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
TI Transdermal iontophoresis of the dopamine agonist 5-OH-DPAT in human skin in vitro
AU Nugroho, Akhmad Kharis; Li, Li; Dijkstra, Durk; Wikstroem, Hakan; Danhof, Meindert; Bouwstra, Joke A.
AB The feasibility of transdermal iontophoretic delivery of a potent dopamine agonist 5-OH-DPAT was studied in vitro in side by side diffusion cells across human stratum corneum (HSC) and dermatomed human skin (DHS) according to the following protocol: 6 h of passive diffusion, 9 h of iontophoresis and 5 h of passive diffusion. The influences of the following parameters on the flux were studied: donor solution pH, NaCl concentration, drug donor concentration, c.d. and skin type. A c.d. of 0.5 mA cm-2 was used, except for one series of expts. to study the c.d. effect. Probably due to the influence of the skin perm-selectivity and the competition with H+, increase in pH from 3 to 5 resulted in a significant increase in flux. Further increase in pH to 6 did not further increase the flux. The iontophoretic transport was found to increase linearly with concentration and c.d., providing a convenient way to manage dose titration for Parkinson's disease therapy. Increase in concentration of NaCl dramatically reduced the flux of 5-OH-DPAT as a result of ion competition to the transport. When DHS was used, the iontophoretic transport was less. Also, with DHS the response in flux profile, by switching the current on and off, was shallower than that with HSC. With the optimum condition, a delivery of 104 μg of 5-OH-DPAT per cm2 patch per h is feasible, indicating that the therapeutic level could be achieved with a smaller patch size than required in case of rotigotine. Thus, based on this in vitro study, transdermal iontophoretic delivery of 5-OH-DPAT is very promising.
SO Journal of Controlled Release (2005), 103(2), 393-403
CODEN: JCREEC; ISSN: 0168-3659
PY 2005

L12 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
TI Compartmental Modeling of Transdermal Iontophoretic Transport: I. In Vitro Model Derivation and Application
AU Nugroho, Akhmad Kharis; Della Pasqua, Oscar; Danhof, Meindert; Bouwstra, Joke A.
AB The objective of this study was to develop a family of compartmental

models to describe in a strictly quant. manner the transdermal iontophoretic transport of drugs in vitro. Two structurally different compartmental models describing the in vitro transport during iontophoresis and one compartmental model describing the in vitro transport in post-iontophoretic period are proposed. These models are based on the mass transfer from the donor compartment to the acceptor compartment via the skin as an intermediate compartment. In these models, transdermal iontophoretic transport is characterized by 5 parameters: (1) kinetic lag time (tL), (2) steady-state flux during iontophoresis (Jss), (3) skin release rate constant (KR), (4) the first-order rate constant of the iontophoretic driving force from the skin to the acceptor compartment (I1), and (5) passive flux in the post-iontophoretic period (Jpas). The developed models were applied to data on the iontophoretic transport in human stratum corneum in vitro of R-apomorphine after pretreatment with phosphate buffered saline pH 7.4 (PBS) and after pretreatment with surfactant (SFC), as well as the iontophoretic transport of 0.5 mg ml-1 rotigotine at pH 5 (RTG). All of the proposed models could be fitted to the transport data of PBS, SFC, and RTG groups both during the iontophoresis and in the post-iontophoretic period. The incorporation of parameter I1 failed to improve the fitting performance of the model. This might indicate a negligible contribution of iontophoretic driving force to the mass transfer in the direction from the skin to the acceptor compartment, although it plays an important role in loading the skin with the drug. The estimated values of Jss of PBS, SFC, and RTG were identical ($p > 0.05$) to the values obtained with the diffusion lag time method. Moreover, time required to achieve steady-state flux can be estimated based on the parameter tL and the reciprocal value of parameter KR. In addition, accumulation of drug mols. in the skin is reflected in a reduction of the value of the KR parameter. The developed in vitro models demonstrated their strength and consistency to describe the drug transport during and post-iontophoresis.

SO Pharmaceutical Research (2004), 21(11), 1974-1984
CODEN: PHREEB; ISSN: 0724-8741

PY 2004

L12 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

TI Iontophoretic delivery of rotigotine for the treatment of Parkinson's disease

IN Wolff, Hans-Michael; Bouwstra, Johanna Aaltje; Li, Gai Ling; Nugroho, Akhmad Kharis

AB By using a composition comprising rotigotine 0.5 to 3 mg/mL and at least one chloride salt in a concentration of 1 to 140 mmol/L, the composition having a pH of 4 to 6.5 in a iontophoretic device for the treatment of Parkinson's disease, it became possible to obtain a rotigotine flux across the human stratum corneum which was higher than the one previously obtained with conventional passive diffusion systems.

SO Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW

PY 2004
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L12 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
TI Transdermal Iontophoresis of Rotigotine Across Human Stratum Corneum in Vitro: Influence of pH and NaCl Concentration
AU Nugroho, Akhmad Kharis; Li, Gai Ling; Danhof, Meindert; Bouwstra, Joke A.
AB The aim of this study was to characterize the influence of pH and NaCl concentration on the transdermal iontophoretic transport of the dopamine receptor agonist rotigotine across human stratum corneum (HSC). Rotigotine transport was studied in vitro in side by side diffusion cells according to the following protocol: 6 h of passive diffusion, 9 h of iontophoresis, and 5 h of passive diffusion. A c.d. of 0.5 mA cm-2 was used. The influence of donor phase pH (4, 5, and 6) and different concns. of NaCl (0.07 and 0.14 M) on rotigotine iontophoretic flux were examined The acceptor phase was phosphate-buffered saline (PBS) at pH 7.4 except in one series of expts. aimed to study the effects of rotigotine solubility on its iontophoretic transport. In this study, PBS at pH 6.2 was used. In sep. studies, 14C-mannitol was used as a marker to determine the role of electro-osmosis during iontophoresis. The estimated iontophoretic steady-state flux (Fluxss) of rotigotine was influenced by the pH of the donor solution At a drug donor concentration of 0.5 mg mL-1, the iontophoretic flux was 30.0 ± 4.2 nmol cm-2 h-1 at pH 6 vs. 22.7 ± 5.5 nmol cm-2 h-1 at pH 5. However, when the donor concentration was increased to 1.4 mg mL-1, no significant difference in iontophoretic rotigotine transport was observed between pH 5 and 6. Increase of NaCl concentration from 0.07 M to 0.14 M resulted in a decrease of the rotigotine Fluxss from 22.7 ± 5.5 nmol cm-2 h-1 to 14.1 ± 4.9 nmol cm-2 h-1. The contribution of electro-osmosis was estimated less than 17%. Probably due to the lipophilic character of the drug, impeding the partitioning of rotigotine from HSC to the acceptor compartment, steady-state transport was not achieved during 9 h of iontophoresis. Both pH and NaCl concentration of the donor phase are crucial on the iontophoretic transport of rotigotine . Electro-repulsion is the main mechanism of the iontophoretic transport of rotigotine.
SO Pharmaceutical Research (2004), 21(5), 844-850
CODEN: PHREEB; ISSN: 0724-8741
PY 2004

L12 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
TI Transdermal iontophoresis of rotigotine: influence of concentration, temperature and current density in human skin in vitro
AU Nugroho, Akhmad Kharis; Li, Gailing; Grossklaus, Arne; Danhof, Meindert; Bouwstra, Joke A.
AB Iontophoretic transport of rotigotine across human stratum corneum (HSC) was studied in vitro in side by side diffusion cells according to the following protocol: 6 h of passive diffusion, 9 h of iontophoresis followed by 5 h of passive diffusion. A c.d. of 0.5 mA cm-2 was applied. The parameters studied were the influence of the rotigotine concentration in donor phase and the influence of the mol. weight of the co-ions. To this end, Na+ was replaced by tetra Et ammonium (TEA+) or tetra Bu ammonium (TBA+) (both at pH 5 and 6). In addition, the influence of the acceptor phase temperature (32° vs. room temperature), the replacement of HSC by dermatomed human skin (DHS), and the relation between drug transport and c.d. were examined The estimated steady-state flux (Fluxss) gradually increased with the drug concentration in the donor phase in a linear manner. The flux was also linearly correlated with the applied c.d. providing a convenient approach to individual dose titration The use of TEA+ as co-ion increased the rotigotine iontophoretic flux

significantly, while TBA+ did not. Replacing HSC by DHS reduced the iontophoretic rotigotine transport, while an increase in temperature to 32° increased the rotigotine flux. The maximum Fluxss achieved was around 80 nmol cm-2 h-1 indicating that by means of iontophoresis, a therapeutic level of rotigotine might be achieved with a reasonable patch size.

SO Journal of Controlled Release (2004), 96(1), 159-167
CODEN: JCREEC; ISSN: 0168-3659

PY 2004

L12 ANSWER 6 OF 20 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

TI Transdermal iontophoresis of the dopamine agonist 5-OH-DPAT in human skin in vitro.

AU Nugroho, Akhmad Kharis; Li, Li; Dijkstra, Durk; Wikstrom, Hakan; Danhof, Meindert; Bouwstra, Joke A. [Reprint Author]

AB The feasibility of transdermal iontophoretic delivery of a potent dopamine agonist 5-OH-DPAT was studied in vitro in side by side diffusion cells across human stratum corneum (HSC) and dermatomed human skin (DHS) according to the following protocol: 6 h of passive diffusion, 9 h of iontophoresis and 5 h of passive diffusion. The influences of the following parameters on the flux were studied: donor solution pH, NaCl concentration, drug donor concentration, current density and skin type. A current density of 0.5 mA cm(-2) was used, except for one series of experiments to study the current density effect.Probably due to the influence of the skin perm-selectivity and the competition with H, increase in pH from 3 to 5 resulted in a significant increase in flux. Further increase in pH to 6 did not further increase the flux. The iontophoretic transport was found to increase linearly with concentration and current density, providing a convenient way to manage dose titration for Parkinson's disease therapy. Increase in concentration of NaCl dramatically reduced the flux of 5-OH-DPAT as a result of ion competition to the transport. When DHS was used, the iontophoretic transport was less. Also, with DHS the response in flux profile, by switching the current on and off, was shallower than that with HSC. With the optimum condition, a delivery of 104 mu g of 5-OH-DPAT per cm(2) patch per hour is feasible, indicating that the therapeutic level could be achieved with a smaller patch size than required in case of rotigotine. Thus, based on this in vitro study, transdermal iontophoretic delivery of 5-OH-DPAT is very promising. (c) 2005 Elsevier B.V. All rights reserved.

SO Journal of Controlled Release, (MAR 21 2005) Vol. 103, No. 2, pp. 393-403.
CODEN: JCREEC. ISSN: 0168-3659.

PY 2005

L12 ANSWER 7 OF 20 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

TI Compartmental modeling of transdermal iontophoretic transport: I. In vitro model derivation and application.

AU Nugroho, Akhmad Kharis; Della Pasqua, Oscar; Danhof, Meindert; Bouwstra, Joke A. [Reprint Author]

AB Purpose. The objective of this study was to develop a family of compartmental models to describe in a strictly quantitative manner the transdermal iontophoretic transport of drugs in vitro. Methods. Two structurally different compartmental models describing the in vitro transport during iontophoresis and one compartmental model describing the in vitro transport in post-iontophoretic period are proposed. These models are based on the mass transfer from the donor compartment to the acceptor compartment via the skin as an intermediate compartment. In these models, transdermal iontophoretic transport is characterized by 5 parameters: 1) kinetic lag time (tL), 2) steady-state flux during iontophoresis (Jss), 3) skin release rate constant (KR), 4) the first-order rate constant of the iontophoretic driving force from the skin to the acceptor compartment (I1), and 5) passive flux in the post-iontophoretic period (Jpas). The developed models were applied to data on the

iontophoretic transport in human stratum corneum in vitro of R-apomorphine after pretreatment with phosphate buffered saline pH 7.4 (PBS) and after pretreatment with surfactant (SFC), as well as the iontophoretic transport of 0.5 mg ml-1 rotigotine at pH 5 (RTG). Results. All of the proposed models could be fitted to the transport data of PBS, SFC, and RTG groups both during the iontophoresis and in the post-iontophoretic period. The incorporation of parameter I1 failed to improve the fitting performance of the model. This might indicate a negligible contribution of iontophoretic driving force to the mass transfer in the direction from the skin to the acceptor compartment, although it plays an important role in loading the skin with the drug. The estimated values of Jss of PBS, SFC, and RTG were identical ($p>0.05$) to the values obtained with the diffusion lag time method. Moreover, time required to achieve steady-state flux can be estimated based on the parameter tL and the reciprocal value of parameter KR. In addition, accumulation of drug molecules in the skin is reflected in a reduction of the value of the KR parameter. Conclusions. The developed in vitro models demonstrated their strength and consistency to describe the drug transport during and post-iontophoresis.

SO Pharmaceutical Research (Dordrecht), (November 2004) Vol. 21, No. 11, pp. 1974-1984. print.
ISSN: 0724-8741 (ISSN print).
PY 2004

L12 ANSWER 8 OF 20 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

TI Transdermal iontophoresis of rotigotine: influence of concentration, temperature and current density in human skin in vitro.

AU Nugroho, Akhmad Kharis; Li, Gailing; Grossklaus, Ame; Danhof, Meindert; Bouwstra, Joke A. [Reprint Author]

AB Iontophoretic transport of rotigotine across human stratum corneum (HSC) was studied in vitro in side by side diffusion cells according to the following protocol: 6 h of passive diffusion, 9 h of iontophoresis followed by 5 h of passive diffusion. A current density of 0.5 mA cm-2 was applied. The parameters studied were the influence of the rotigotine concentration in donor phase and the influence of the molecular weight of the co-ions. To this end, Na+ was replaced by tetra ethyl ammonium (TEA+) or tetra butyl ammonium (TBA+) (both at pH 5 and 6). In addition, the influence of the acceptor phase temperature (32 degreeC versus room temperature), the replacement of HSC by dermatomed human skin (DHS), and the relation between drug transport and current density were examined. The estimated steady-state flux (FluxSS) gradually increased with the drug concentration in the donor phase in a linear manner. The flux was also linearly correlated with the applied current density providing a convenient approach to individual dose titration. The use of TEA+ as co-ion increased the rotigotine iontophoretic flux significantly, while TBA+ did not. Replacing HSC by DHS reduced the iontophoretic rotigotine transport, while an increase in temperature to 32 degreeC increased the rotigotine flux. The maximum FluxSS achieved was around 80 nmol cm-2 h-1 indicating that by means of iontophoresis, a therapeutic level of rotigotine might be achieved with a reasonable patch size.

SO Journal of Controlled Release, (April 16 2004) Vol. 96, No. 1, pp. 159-167. print.
ISSN: 0168-3659 (ISSN print).
PY 2004

L12 ANSWER 9 OF 20 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

TI Transdermal iontophoresis of rotigotine across human stratum corneum in vitro: Influence of pH and NaCl concentration.

AU Nugroho, Akhmad Kharis; Li, Gai ng; Danhof, Meindert; Bouwstra, Joke A. [Reprint Author]

AB Purpose. The aim of this study was to characterize the influence of pH

and NaCl concentration on the transdermal iontophoretic transport of the dopamine receptor agonist rotigotine across human stratum corneum (HSC). Methods. Rotigotine transport was studied in vitro in side by side diffusion cells according to the following protocol: 6 h of passive diffusion, 9 h of iontophoresis , and 5 h of passive diffusion. A current density of 0.5 mA cm-2 was used. The influence of donor phase pH (4, 5, and 6) and different concentrations of NaCl (0.07 and 0.14 M) on rotigotine iontophoretic flux were examined. The acceptor phase was phosphate-buffered saline (PBS) at pH 7.4 except in one series of experiments aimed to study the effects of rotigotine solubility on its iontophoretic transport. In this study, PBS at pH 6.2 was used. In separate studies, 14C-mannitol was used as a marker to determine the role of electro-osmosis during iontophoresis. Results. The estimated iontophoretic steady-state flux (Fluxss) of rotigotine was influenced by the pH of the donor solution. At a drug donor concentration of 0.5 mg ml-1, the iontophoretic flux was 30.0 +/- 4.2 nmol cm-2 h-1 at pH 6 vs. 22.7 +/- 5.5 nmol cm-2 h-1 at pH 5. However, when the donor concentration was increased to 1.4 mg ml-1, no significant difference in iontophoretic rotigotine transport was observed between pH 5 and 6. Increase of NaCl concentration from 0.07 M to 0.14 M resulted in a decrease of the rotigotine Fluxss from 22.7 +/- 5.5 nmol cm-2 h-1 to 14.1 +/- 4.9 nmol cm-2 h-1. The contribution of electro-osmosis was estimated less than 17%. Probably due to the lipophilic character of the drug, impeding the partitioning of rotigotine from HSC to the acceptor compartment, steady-state transport was not achieved during 9 h of iontophoresis. Conclusions. Both pH and NaCl concentration of the donor phase are crucial on the iontophoretic transport of rotigotine. Electro-repulsion is the main mechanism of the iontophoretic transport of rotigotine.

SO Pharmaceutical Research (Dordrecht), (May 2004) Vol. 21, No. 5, pp. 844-850. print.
ISSN: 0724-8741 (ISSN print).
PY 2004

L12 ANSWER 10 OF 20 MEDLINE on STN

TI Transdermal iontophoresis of the dopamine agonist 5-OH-DPAT in human skin in vitro.

AU Nugroho Akhmad Kharis; Li Li; Dijkstra Durk; Wikstrom Hakan; Danhof Meindert; Bouwstra Joke A

AB The feasibility of transdermal iontophoretic delivery of a potent dopamine agonist 5-OH-DPAT was studied in vitro in side by side diffusion cells across human stratum corneum (HSC) and dermatomed human skin (DHS) according to the following protocol: 6 h of passive diffusion, 9 h of iontophoresis and 5 h of passive diffusion. The influences of the following parameters on the flux were studied: donor solution pH, NaCl concentration, drug donor concentration, current density and skin type. A current density of 0.5 mA cm(-2) was used, except for one series of experiments to study the current density effect. Probably due to the influence of the skin perm-selectivity and the competition with H(+), increase in pH from 3 to 5 resulted in a significant increase in flux. Further increase in pH to 6 did not further increase the flux. The iontophoretic transport was found to increase linearly with concentration and current density, providing a convenient way to manage dose titration for Parkinson's disease therapy. Increase in concentration of NaCl dramatically reduced the flux of 5-OH-DPAT as a result of ion competition to the transport. When DHS was used, the iontophoretic transport was less. Also, with DHS the response in flux profile, by switching the current on and off, was shallower than that with HSC. With the optimum condition, a delivery of 104 microg of 5-OH-DPAT per cm(2) patch per hour is feasible, indicating that the therapeutic level could be achieved with a smaller patch size than required in case of rotigotine. Thus, based on this in vitro

study, transdermal iontophoretic delivery of 5-OH-DPAT is very promising.

SO Journal of controlled release : official journal of the Controlled Release Society, (2005 Mar 21) Vol. 103, No. 2, pp. 393-403. Journal code: 8607908. ISSN: 0168-3659.

PY 2005

L12 ANSWER 11 OF 20 MEDLINE on STN

TI Compartmental modeling of transdermal iontophoretic transport: I. In vitro model derivation and application.

AU Nugroho Akhmad Kharis; Pasqua Oscar Della; Danhof Meindert; Bouwstra Joke A

AB PURPOSE: The objective of this study was to develop a family of compartmental models to describe in a strictly quantitative manner the transdermal iontophoretic transport of drugs in vitro. METHODS: Two structurally different compartmental models describing the in vitro transport during iontophoresis and one compartmental model describing the in vitro transport in post-iontophoretic period are proposed. These models are based on the mass transfer from the donor compartment to the acceptor compartment via the skin as an intermediate compartment. In these models, transdermal iontophoretic transport is characterized by 5 parameters: 1) kinetic lag time (tL), 2) steady-state flux during iontophoresis (Jss), 3) skin release rate constant (K(R)), 4) the first-order rate constant of the iontophoretic driving force from the skin to the acceptor compartment (I1), and 5) passive flux in the post-iontophoretic period (Jpas). The developed models were applied to data on the iontophoretic transport in human stratum corneum in vitro of R-apomorphine after pretreatment with phosphate buffered saline pH 7.4 (PBS) and after pretreatment with surfactant (SFC), as well as the iontophoretic transport of 0.5 mg ml(-1) rotigotine at pH 5 (RTG). RESULTS: All of the proposed models could be fitted to the transport data of PBS, SFC, and RTG groups both during the iontophoresis and in the post-iontophoretic period. The incorporation of parameter I1 failed to improve the fitting performance of the model. This might indicate a negligible contribution of iontophoretic driving force to the mass transfer in the direction from the skin to the acceptor compartment, although it plays an important role in loading the skin with the drug. The estimated values of Jss of PBS, SFC, and RTG were identical ($p > 0.05$) to the values obtained with the diffusion lag time method. Moreover, time required to achieve steady-state flux can be estimated based on the parameter tL and the reciprocal value of parameter K(R). In addition, accumulation of drug molecules in the skin is reflected in a reduction of the value of the K(R) parameter. CONCLUSIONS: The developed in vitro models demonstrated their strength and consistency to describe the drug transport during and post-iontophoresis.

SO Pharmaceutical research, (2004 Nov) Vol. 21, No. 11, pp. 1974-84. Journal code: 8406521. ISSN: 0724-8741.

PY 2004

L12 ANSWER 12 OF 20 MEDLINE on STN

TI Transdermal iontophoresis of rotigotine across human stratum corneum in vitro: influence of pH and NaCl concentration.

AU Nugroho Akhmad Kharis; Li Gai Ling; Danhof Meindert; Bouwstra Joke A

AB PURPOSE: The aim of this study was to characterize the influence of pH and NaCl concentration on the transdermal iontophoretic transport of the dopamine receptor agonist rotigotine across human stratum corneum (HSC). METHODS: Rotigotine transport was studied in vitro in side by side diffusion cells according to the following protocol: 6 h of passive diffusion, 9 h of iontophoresis, and 5 h of passive diffusion. A current density of 0.5 mA cm(-2) was used. The influence of donor phase pH (4, 5, and 6) and different concentrations of NaCl (0.07 and 0.14 M) on rotigotine iontophoretic

flux were examined. The acceptor phase was phosphate-buffered saline (PBS) at pH 7.4 except in one series of experiments aimed to study the effects of rotigotine solubility on its iontophoretic transport. In this study, PBS at pH 6.2 was used. In separate studies. 14C-mannitol was used as a marker to determine the role of electro-osmosis during iontophoresis. RESULTS: The estimated iontophoretic steady-state flux (Flux(ss)) of rotigotine was influenced by the pH of the donor solution. At a drug donor concentration of 0.5 mg ml(-1), the iontophoretic flux was 30.0 +/- 4.2 nmol cm(-2) h(-1) at pH 6 vs. 22.7 +/- 5.5 nmol cm(-2) h(-1) at pH 5. However, when the donor concentration was increased to 1.4 mg ml(-1), no significant difference in iontophoretic rotigotine transport was observed between pH 5 and 6. Increase of NaCl concentration from 0.07 M to 0.14 M resulted in a decrease of the rotigotine Flux(ss) from 22.7 +/- 5.5 nmol cm(-2) h(-1) to 14.1 +/- 4.9 nmol cm(-2) h(-1). The contribution of electro-osmosis was estimated less than 17%. Probably due to the lipophilic character of the drug, impeding the partitioning of rotigotine from HSC to the acceptor compartment, steady-state transport was not achieved during 9 h of iontophoresis. CONCLUSIONS: Both pH and NaCl concentration of the donor phase are crucial on the iontophoretic transport of rotigotine. Electro-repulsion is the main mechanism of the iontophoretic transport of rotigotine.

SO Pharmaceutical research, (2004 May) Vol. 21, No. 5, pp. 844-50. Journal code: 8406521. ISSN: 0724-8741.

PY 2004

L12 ANSWER 13 OF 20 MEDLINE on STN

TI Transdermal iontophoresis of rotigotine: influence of concentration, temperature and current density in human skin in vitro.

AU Nugroho Akhmad Kharis; Li Gailing; Grossklaus Arne; Danhof Meindert; Bouwstra Joke A

AB Iontophoretic transport of rotigotine across human stratum corneum (HSC) was studied in vitro in side by side diffusion cells according to the following protocol: 6 h of passive diffusion, 9 h of iontophoresis followed by 5 h of passive diffusion. A current density of 0.5 mA cm(-2) was applied. The parameters studied were the influence of the rotigotine concentration in donor phase and the influence of the molecular weight of the co-ions. To this end, Na(+) was replaced by tetra ethyl ammonium (TEA(+)) or tetra butyl ammonium (TBA(+)) (both at pH 5 and 6). In addition, the influence of the acceptor phase temperature (32 degrees C versus room temperature), the replacement of HSC by dermatomed human skin (DHS), and the relation between drug transport and current density were examined. The estimated steady-state flux (Flux(ss)) gradually increased with the drug concentration in the donor phase in a linear manner. The flux was also linearly correlated with the applied current density providing a convenient approach to individual dose titration. The use of TEA(+) as co-ion increased the rotigotine iontophoretic flux significantly, while TBA(+) did not. Replacing HSC by DHS reduced the iontophoretic rotigotine transport, while an increase in temperature to 32 degrees C increased the rotigotine flux. The maximum Flux(ss) achieved was around 80 nmol cm(-2) h(-1) indicating that by means of iontophoresis, a therapeutic level of rotigotine might be achieved with a reasonable patch size.

SO Journal of controlled release : official journal of the Controlled Release Society, (2004 Apr 16) Vol. 96, No. 1, pp. 159-67. Journal code: 8607908. ISSN: 0168-3659.

PY 2004

L12 ANSWER 14 OF 20 EMBASE

TI Iontophoresis - An approach for controlled drug delivery: A review.

AU Dixit N.; Bali V.; Baboota S.; Ahuja A.; Ali J.
AB The recent approval of lidocaine hydrochloride and epinephrine combined iontophoretic patch (Lidosite® Vysteris Inc.) for localized pain treatment by FDA has invigorated the gaining interest in iontophoretic drug delivery systems for the transdermal delivery of drugs. This technique of facilitated movement of ions across a membrane under the influence of an externally applied electric potential difference, is one of the most promising physical skin penetration enhancing method. The rationale behind using this technique is the capability of this method to increase the systemic delivery of high molecular weight compounds with controlled input kinetics and minimum inter-subject variability, which is otherwise achieved only when parentral route of administration is used. Recently, good permeation of larger peptides like insulin has been achieved through this technique in combination with chemical enhancers. This review briefly describes the factors which affect iontophoretic drug delivery and summarizes the studies conducted recently using this technique in order to achieve higher systemic absorption of the drugs having low passive diffusion otherwise. The effect of permeation enhancers (chemical enhancers) on iontophoretic flux of drugs has also been described. Present review also provides an insight into reverse iontophoresis. Various parameters which affect the transdermal absorption of drugs through iontophoresis like drug concentration, polarity of drugs, pH of donor solution, presence of co-ions, ionic strength, electrode polarity etc. have also been reviewed in detail. .COPYRGT. 2007 Bentham Science Publishers Ltd.
SO Current Drug Delivery, (2007) Vol. 4, No. 1, pp. 1-10. .
Refs: 105
ISSN: 1567-2018
PY 2007

L12 ANSWER 15 OF 20 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
TI Elastic vesicles as a tool for dermal and transdermal delivery.
AU Honeywell-Nguyen P.L.; Groenink H.W.W.; Bouwstra J.A.
AB The main problem in delivery of drugs across the skin is the barrier function of the skin, which is located in the outermost layer of the skin, the stratum corneum. The stratum corneum consists of corneocytes surrounded by lipid layers, the so-called lipid lamellae. When applying drugs onto the skin, the major penetration pathway is the tortuous intercellular route along the lipid lamellae. In order to increase the number of drugs administered via the transdermal route, novel drug delivery systems have to be designed. Among these systems are iontophoresis, electroporation, microneedles, and vesicular systems. Copyright .COPYRGT. Informa Healthcare.
SO Journal of Liposome Research, (1 Sep 2006) Vol. 16, No. 3, pp. 273-280. .
Refs: 11
ISSN: 0898-2104 E-ISSN: 1532-2394 CODEN: JLREE7
PY 2006

L12 ANSWER 16 OF 20 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
TI Transdermal iontophoresis.
AU Priya B.; Rashmi T.; Bozena M.
AB Iontophoresis is a technique used to enhance the transdermal delivery of compounds through the skin via the application of a small electric current. By the process of electromigration and electro-osmosis, iontophoresis increases the permeation of charged and neutral compounds, and offers the option for programmed drug delivery. Interest in this field of research has led to the successful delivery of both low (lidocaine) and high molecular drugs, such as peptides (e.g., luteinising hormone releasing hormone, nafarelin and insulin). Combinations of iontophoresis with chemical enhancers, electroporation and sonophoresis have been tested in order to further increase transdermal

drug permeation and decrease possible side effects. In addition, rapid progress in the fields of microelectronics, nanotechnology and miniaturisation of devices is leading the way to more sophisticated iontophoretic devices, allowing improved designs with better control of drug delivery. Recent successful designing of the fentanyl E-TRANS® iontophoretic system have provided encouraging results. This review will discuss basic concepts, principles and applications of this delivery technique. .COPYRGT. 2006 Ashley Publications.

SO Expert Opinion on Drug Delivery, (2006) Vol. 3, No. 1, pp. 127-138. .
Refs: 79
ISSN: 1742-5247

PY 2006

L12 ANSWER 17 OF 20 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

TI Compartmental modeling of transdermal iontophoretic transport: I. In vitro model derivation and application.

AU Nugroho A.K.; Della Pasqua O.; Danhof M.; Bouwstra J.A.

AB Purpose. The objective of this study was to develop a family of compartmental models to describe in a strictly quantitative manner the transdermal iontophoretic transport of drugs in vitro. Methods. Two structurally different compartmental models describing the in vitro transport during iontophoresis and one compartmental model describing the in vitro transport in post-iontophoretic period are proposed. These models are based on the mass transfer from the donor compartment to the acceptor compartment via the skin as an intermediate compartment. In these models, transdermal iontophoretic transport is characterized by 5 parameters: 1) kinetic lag time (t(L)), 2) steady-state flux during iontophoresis (J(ss)), 3) skin release rate constant (K(R)), 4) the first-order rate constant of the iontophoretic driving force from the skin to the acceptor compartment (I (1)), and 5) passive flux in the post-iontophoretic period (J (pas)). The developed models were applied to data on the iontophoretic transport in human stratum corneum in vitro of R-apomorphine after pretreatment with phosphate buffered saline pH 7.4 (PBS) and after pretreatment with surfactant (SFC), as well as the iontophoretic transport of 0.5 mg ml (-1) rotigotine at pH 5 (RTG). Results. All of the proposed models could be fitted to the transport data of PBS, SFC, and RTG groups both during the iontophoresis and in the post-iontophoretic period. The incorporation of parameter I(1) failed to improve the fitting performance of the model. This might indicate a negligible contribution of iontophoretic driving force to the mass transfer in the direction from the skin to the acceptor compartment, although it plays an important role in loading the skin with the drug. The estimated values of J(ss) of PBS, SFC, and RTG were identical ($p > 0.05$) to the values obtained with the diffusion lag time method. Moreover, time required to achieve steady-state flux can be estimated based on the parameter t(L) and the reciprocal value of parameter K(R). In addition, accumulation of drug molecules in the skin is reflected in a reduction of the value of the K(R) parameter. Conclusions. The developed in vitro models demonstrated their strength and consistency to describe the drug transport during and post-iontophoresis. .COPYRGT. 2004 Springer Science+Business Media, Inc.

SO Pharmaceutical Research, (2004) Vol. 21, No. 11, pp. 1974-1984. .
Refs: 26
ISSN: 0724-8741 CODEN: PHREEB

PY 2004

L12 ANSWER 18 OF 20 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

TI Transdermal iontophoresis of the dopamine agonist 5-OH-DPAT in human skin in vitro.

AU Nugroho A.K.; Li L.; Dijkstra D.; Wikstrom H.; Danhof M.; Bouwstra J.A.

AB The feasibility of transdermal iontophoretic delivery of a potent dopamine agonist 5-OH-DPAT was studied in vitro in side by side diffusion cells across human stratum corneum (HSC) and dermatomed human skin (DHS) according to the following protocol: 6 h of passive diffusion, 9 h of iontophoresis and 5 h of passive diffusion. The influences of the following parameters on the flux were studied: donor solution pH, NaCl concentration, drug donor concentration, current density and skin type. A current density of 0.5 mA cm(-2) was used, except for one series of experiments to study the current density effect. Probably due to the influence of the skin perm-selectivity and the competition with H(+), increase in pH from 3 to 5 resulted in a significant increase in flux. Further increase in pH to 6 did not further increase the flux. The iontophoretic transport was found to increase linearly with concentration and current density, providing a convenient way to manage dose titration for Parkinson's disease therapy. Increase in concentration of NaCl dramatically reduced the flux of 5-OH-DPAT as a result of ion competition to the transport. When DHS was used, the iontophoretic transport was less. Also, with DHS the response in flux profile, by switching the current on and off, was shallower than that with HSC. With the optimum condition, a delivery of 104 μg of 5-OH-DPAT per cm(2) patch per hour is feasible, indicating that the therapeutic level could be achieved with a smaller patch size than required in case of rotigotine. Thus, based on this in vitro study, transdermal iontophoretic delivery of 5-OH-DPAT is very promising.

SO Journal of Controlled Release, (21 Mar 2005) Vol. 103, No. 2, pp. 393-403.

Refs: 33

ISSN: 0168-3659 CODEN: JCREEC

PY 2005

L12 ANSWER 19 OF 20 EMBASE

TI Transdermal iontophoresis of rotigotine across human stratum corneum in vitro: Influence of pH and NaCl concentration.

AU Nugroho A.K.; Gai L.L.; Danhof M.; Bouwstra J.A.

AB Purpose. The aim of this study was to characterize the influence of pH and NaCl concentration on the transdermal iontophoretic transport of the dopamine receptor agonist rotigotine across human stratum corneum (HSC). Methods. Rotigotine transport was studied in vitro in side by side diffusion cells according to the following protocol: 6 h of passive diffusion, 9 h of iontophoresis , and 5 h of passive diffusion. A current density of 0.5 mA cm (-2) was used. The influence of donor phase pH (4, 5, and 6) and different concentrations of NaCl (0.07 and 0.14 M) on rotigotine iontophoretic flux were examined. The acceptor phase was phosphate-buffered saline (PBS) at pH 7.4 except in one series of experiments aimed to study the effects of rotigotine solubility on its iontophoretic transport. In this study, PBS at pH 6.2 was used. In separate studies, (14)C-mannitol was used as a marker to determine the role of electro-osmosis during iontophoresis. Results. The estimated iontophoretic steady-state flux (Flux(ss)) of rotigotine was influenced by the pH of the donor solution. At a drug donor concentration of 0.5 mg ml(-1), the iontophoretic flux was 30.0 ± 4.2 nmol cm (-2) h(-1) at pH 6 vs. 22.7 ± 5.5 nmol cm(-2) h(-1) at pH 5. However, when the donor concentration was increased to 1.4 mg ml(-1), no significant difference in iontophoretic rotigotine transport was observed between pH 5 and 6. Increase of NaCl concentration from 0.07 M to 0.14 M resulted in a decrease of the rotigotine Flux(ss) from 22.7 ± 5.5 nmol cm(-2) h(-1) to 14.1 ± 4.9 nmol cm(-2) h(-1). The contribution of electro-osmosis was estimated less than 17%. Probably due to the lipophilic character of the drug, impeding the partitioning of

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SO Pharmaceutical Research, (2004) Vol. 21, No. 5, pp. 844-850. .
Refs: 32
ISSN: 0724-8741 CODEN: PHREEB

PY 2004

L12 ANSWER 20 OF 20 EMBASE

TI Transdermal iontophoresis of rotigotine: Influence of concentration, temperature and current density in human skin in vitro.

AU Nugroho A.K.; Li G.; Grossklaus A.; Danhof M.; Bouwstra J.A.

AB Iontophoretic transport of rotigotine across human stratum corneum (HSC) was studied in vitro in side by side diffusion cells according to the following protocol: 6 h of passive diffusion, 9 h of iontophoresis followed by 5 h of passive diffusion. A current density of 0.5 mA cm(-2) was applied. The parameters studied were the influence of the rotigotine concentration in donor phase and the influence of the molecular weight of the co-ions. To this end, Na(+) was replaced by tetra ethyl ammonium (TEA(+)) or tetra butyl ammonium (TBA(+)) (both at pH 5 and 6). In addition, the influence of the acceptor phase temperature (32°C versus room temperature), the replacement of HSC by dermatomed human skin (DHS), and the relation between drug transport and current density were examined. The estimated steady-state flux (Flux(ss)) gradually increased with the drug concentration in the donor phase in a linear manner. The flux was also linearly correlated with the applied current density providing a convenient approach to individual dose titration. The use of TEA(+) as co-ion increased the rotigotine iontophoretic flux significantly, while TBA(+) did not. Replacing HSC by DHS reduced the iontophoretic rotigotine transport, while an increase in temperature to 32°C increased the rotigotine flux. The maximum Flux (ss) achieved was around 80 nmol cm(-2) h(-1) indicating that by means of iontophoresis, a therapeutic level of rotigotine might be achieved with a reasonable patch size.

SO Journal of Controlled Release, (16 Apr 2004) Vol. 96, No. 1, pp. 159-167. .
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PY 2004

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